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Authors

Hobson, Kristina G
Havel, Peter J
McMurtry, Addison L
et al.

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Circulating Leptin and Cortisol After Burn Injury: Loss of Diurnal Pattern

Kristina G. Hobson, MD,* Peter J. Havel, DVM, PhD,†
Addison L. McMurtry, MD,* Mary Beth Lawless, RN,* Tina L. Palmieri, MD,*
David D. Greenhalgh, MD*

Leptin, a hormone involved in appetite and metabolic energy expenditure, could have a role in the reduced appetite and/or energy expenditure after burn injury. In this study, the diurnal pattern of circulating leptin concentrations was compared with body mass index (BMI), sex, glucose, insulin, and the diurnal cortisol rhythm in burn patients. Plasma samples were collected at 12:00 PM and 02:00 AM from severely burned adults and children. Circulating leptin, insulin, and cortisol were measured by radioimmunoassay. Results were compared with previously published data from healthy control subjects. Overall, plasma leptin levels were lower in burn patients (5.7 ± 1.2 ng/mL) compared with control subjects (10.5 ± 1.7 ng/mL, $P = .02$). The normal nocturnal increase of circulating leptin concentrations observed in control subjects was completely absent in burn patients. Cortisol levels were higher in burn patients (20.4 ± 1.0 mg/dL) than in control subjects (9.8 ± 1.6 mg/dL, $P < .0001$) and the normal circadian decrease of circulating cortisol levels was markedly blunted in burn patients. Plasma cortisol did not correlate with circulating leptin levels. Plasma insulin and plasma glucose levels were significantly elevated in burn patients and the insulin:glucose ratio was dramatically increased compared with control subjects. Patients with burn injuries exhibited significantly decreased circulating leptin levels. This decrease may be the result of marked insulin resistance, as suggested by the elevated insulin to glucose ratio in burn patients. The loss of the diurnal pattern in burn patients is likely to result from the continuous nutritional supplementation. Because low leptin levels should induce appetite, burn-related anorexia is probably controlled by other regulatory systems. (*J Burn Care Rehabil* 2004;25:491–499)

Burn injury produces profound metabolic changes, including significant increases in catecholamines,¹ corticosteroids,² and a generalized catabolic response. Despite a dramatic increase in energy expenditure, patients do not compensate by increasing their nutritional intake. In fact, patients suffering from burn injuries are more likely to have suppressed appetites. Burn care providers are challenged to con-

vince patients to ingest calories sufficient to satisfy their markedly increased nutritional requirements.

The mediators of this maladaptive response are not clearly understood. Leptin is a hormone produced by adipose tissue and is involved in the regulation of appetite, energy intake, and metabolic energy expenditure.³ Leptin production increases after a meal to contribute to the suppression of appetite, whereas fasting reduces leptin levels to stimulate appetite. Humans and animals that have mutations in the leptin gene or in the leptin receptor are hyperphagic and exhibit marked early-onset obesity.⁴ The hyperphagia and obesity associated with leptin deficiency are reversed by exogenous leptin administration.⁵ These effects are likely centrally mediated because the administration of leptin into the central nervous system reduces food intake and increases sympathetic nervous system activity in rhesus monkeys.⁶ Furthermore, prolonged moderate caloric deficits normally

*From the *Departments of Surgery, Shriners Hospitals for Children of Northern California and University of California Davis Medical Center, Sacramento; and †Department of Nutrition, University of California, Davis, California.*

Address correspondence to Dr. David G. Greenhalgh, Chief, Department of Burn Surgery, Shriners Hospitals for Children Northern California, 2426 Stockton Boulevard, Sacramento, California 95817.

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lead to increased hunger. This increase of hunger during a caloric deficit in human subjects is correlated with decreased circulating leptin levels, which are suppressed as a result of the restricted energy intake.⁷ Thus, normal leptin production and action are required to maintain a balance of energy intake and expenditure.

Circulating leptin concentrations normally exhibit a diurnal pattern, with a midmorning nadir and a nocturnal peak that typically occurs between midnight and 2 AM in subjects consuming meals on a regular schedule.⁸ The diurnal pattern is not present in fasting subjects and, in fact, leptin concentrations will decrease and remain low until the subjects eat a meal.⁹ The diurnal pattern of leptin secretion does not appear to be directly related to the circadian rhythm of the hypothalamic–pituitary–adrenal axis because the timing of the nocturnal leptin peak is shifted by the timing of meal consumption, independently of any effect on circulating cortisol concentrations.¹⁰ The largest increase of leptin is observed approximately 4 to 6 hours after each meal, and the consumption of high-carbohydrate meals increases the entire 24-hour leptin profile relative to consumption of high-fat meals.¹¹ The effects of fasting and eating on circulating leptin concentrations are largely mediated by changes in insulin secretion.³ Insulin increases leptin production via its effects to increase glucose metabolism in adipocytes.¹² Insulin-mediated glucose metabolism also appears to regulate circulating leptin concentrations in humans¹³ and thereby has a major role in mediating the diurnal pattern of circulating leptin.¹⁴

Although leptin levels have not been previously examined in burn patients, studies of leptin levels in patients with sepsis have reported dramatically increased fasting leptin concentrations as well as increased plasma levels of a number of other hormones and inflammatory mediators, including cortisol and interleukin-6.^{15–17} Increased leptin levels in some of these patients with sepsis were accompanied by a complete loss of the typical diurnal pattern of leptin secretion.¹⁵ There is some evidence that the administration of cytokines, such as tumor necrosis factor- α ¹⁸ and interleukins,¹⁹ or glucocorticoids^{20,21} can increase circulating leptin levels. Burn patients typically are severely stressed and exhibit high levels of these inflammatory mediators. It is therefore possible that increased levels of cytokines or glucocorticoids could result in a disruption of the diurnal pattern of leptin secretion in patients with burn injury.

If elevated leptin levels or a loss of normal diurnal rhythm of leptin secretion were found to be present in burn patients, the alterations could contribute to

the loss of appetite and markedly increased nutritional requirements that frequently complicate burn convalescence. To investigate a potential role for leptin in the appetite reduction and metabolic derangements in burn convalescence, we measured circulating leptin concentrations at the times of the expected nadir and peak of leptin levels in patients recovering from acute burn injury. We also examined the relationship of plasma leptin levels in burn patients to factors that could potentially alter leptin homeostasis, including body mass index (BMI) and circulating cortisol, insulin, and glucose concentrations. Because we admit no “control” population for comparison with burn patients, we used data obtained from one of the authors (P.J.H.) previously published works for controls in the adult population. These “controls” were normal volunteers who were housed in a clinical metabolic laboratory for the determination of normal values.²² Pediatric patients were compared with previously published data.²³ The same techniques were used for the burn patients as those of the controls.

MATERIALS AND METHODS

Subjects and Sample Collection

Subjects were recruited from the Burn Intensive Care Units at the University of California Davis Medical Center and the Shriners Hospitals for Children Northern California in Sacramento. The study protocol was approved by the Institutional Human Subjects Review Committee of the University of California, Davis. All subjects or their parents provided informed consent. Patients with 20% TBSA burns or greater were enrolled in the study. Patients with known diabetes or those receiving exogenous growth hormone therapy were excluded.

Initial baseline data included age, sex, and percentage TBSA burned. Body mass index and weight were recorded as close to the time of admission as possible in an effort to prevent inaccuracies caused by resuscitation-induced edema. Caloric goals were estimated by routine measurements of resting energy expenditure and nitrogen balance. Total caloric intake, protein intake, and percent of goal were recorded. Blood samples were drawn at 2:00 AM and 12:00 PM. These times were chosen to approximate the timing of peak and trough leptin levels as described in normal subjects.¹¹ Blood samples were drawn twice daily every day for the first week that each patient was enrolled in the study and twice daily, twice a week thereafter. All other medical care was provided per standard hospital protocol.

Normal leptin and cortisol values for nonobese adult men and women from our previously published study²² were included for comparison with results measured in burn patients. Their levels were drawn at multiple time points but only values at 12 noon and 2 AM were used for comparison with burn patients. Normal values by age and sex for the pediatric patients were derived from a study by García-Mayor et al²³ in which circulating leptin concentrations were determined using the same assay as the current study.^{23,24} The amplitude of the diurnal variation of leptin and cortisol and the percent changes from nadir to peak levels were compared with the same changes we previously published in a study of normal weight women.¹¹ Although this previous study determined the cortisol and leptin patterns only in adult female patients, proportional changes of daily cortisol and leptin are similar between men and women^{25,26} and between adults and children.^{27,28} These normal values were therefore used for comparison to all patients in both the pediatric and the adult groups. We realize that these control values were derived from other studies; however, control patients are not available in a burn center. The adult values were derived from the same laboratory, and the pediatric values used the same technique.

Assays and Data Analysis

Plasma was collected in tubes containing ethylenediamine tetraacetic acid, immediately centrifuged, and stored at -70°C until analyzed. Plasma glucose was measured with a YSI 2300 StatPlus Glucose Analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma leptin was measured with a radioimmunoassay for human leptin with reagents from Linco Research (St. Charles, MO) as previously described.²⁴ Plasma cortisol was measured by radioimmunoassay with an Immuchem-coated tube kit (ICN Biomedical, Costa Mesa, CA). Plasma insulin levels were determined with a radioimmunoassay for human insulin²⁹ with minor modifications and using human insulin standards from Linco Research.

Because the concentrations of leptin and other parameters measured did not change significantly over the course of time, the concentrations from blood collections from all time points over the course of the study were averaged, and these mean values were then used for the analysis. Results are expressed as the mean \pm standard error of the mean. The Student's *t*-test was used for comparison of the values for control and study groups. Trends were assessed by linear regression and analysis of variance. Results with a corresponding *P* value of less than .05 were considered statistically significant.

RESULTS

Patient Characteristics

A total of 20 patients were enrolled during an 18-month period, including 13 children (age, 2.5 to 12 years) and 7 adults (age, 19 to 77 years; see Table 1). Gender was fairly equally distributed between groups, with 43% and 54% females in the adult and pediatric groups, respectively. The mean size of burn injury was 37% TBSA (range, 21% to 80%). All patients received continuous caloric replacement via postpyloric tube feedings during the first several weeks of hospitalization and, thus, for the majority of the study. Feeding tubes routinely were placed as soon as possible after admission, and feedings were advanced rapidly *to goal*. All patients tolerated tube feedings at a rate that satisfied their caloric goal, as assessed by frequent measurements of resting energy expenditures and nitrogen balance (data not shown).

Body Mass Index

Patients were generally not obese, with a mean BMI for adults of $26.4 \pm 2.6 \text{ kg/m}^2$. Only one patient (an adult woman) had a BMI of greater than 31 kg/m^2 . Body mass index and leptin levels were positively correlated ($R^2 = .62$, $P = .04$) in adults (Figure 1). The BMI data were obtained at admission and did not change significantly throughout the course of the study. Children were not included in the analysis of

Table 1. Characteristics of burned patients

	Men (n = 4)	Women (n = 3)	Boys (n = 6)	Girls (n = 7)
Age, years	42 (18–77)	34 (23–41)	8 (5–12)	5 (3–12)
%TBSA burn	43.0 \pm 9.2	35.0 \pm 7.5	38.6 \pm 4.4	32.6 \pm 3.1
BMI, kg/m ²	23.5 \pm 2.0	30.1 \pm 5.3	16.6 \pm 0.8	17.1 \pm 1.2

BMI, body mass index, TBSA, total body surface area.
Values are expressed as mean (range) or mean \pm SEM.

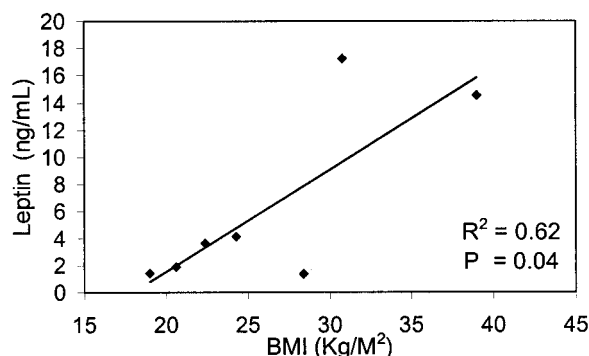


Figure 1. Correlation between mean circulating leptin concentrations and preresuscitation body mass index (BMI) for adult patients with burn injury. The direct positive relationship shown here is similar to that observed in normal healthy adults.

the relationship between BMI and leptin because the relationship between body weight and height in children is different from that in adults. The mean BMI for the children was $16.6 \pm 0.8 \text{ kg/m}^2$ for the boys and $17.1 \pm 1.2 \text{ kg/m}^2$ for the girls, which would be considered very lean in adults.

Leptin

The burn patients in our study had significantly lower leptin levels overall ($P < .02$) when compared with normal healthy control subjects ($5.7 \pm 1.2 \text{ ng/mL}$; range, 1.4–20 ng/mL compared with $10.5 \pm 1.7 \text{ ng/mL}$; range, 1.7–29.7 ng/mL). To correct for the effects of differences in body adiposity, circulating leptin concentrations were standardized by dividing them by the BMI (Figures 1 and 2). Although the difference between normal subjects and burn subjects after normalization was smaller, it remained statistically significant, with a mean leptin/BMI in burned subjects of 0.30 ± 0.04 compared with a mean leptin/BMI of 0.44 ± 0.07 in control subjects ($P = .04$).

We then separated the subjects into four groups based on the two potentially confounding variables of age and sex (Figure 2). We were interested to find that adult women with burn injuries exhibited the most marked decrease of leptin, with leptin/BMI values that were only $50 \pm 20\%$ of levels in unburned women ($n = 3$). Normally, women have higher leptin levels than men; in these preliminary studies, their leptin levels decreased to those of men and children. It is important to remember that these results were found in only three women; therefore, the findings must be corroborated with more patients. Leptin levels in adult men with burn injuries were not significantly

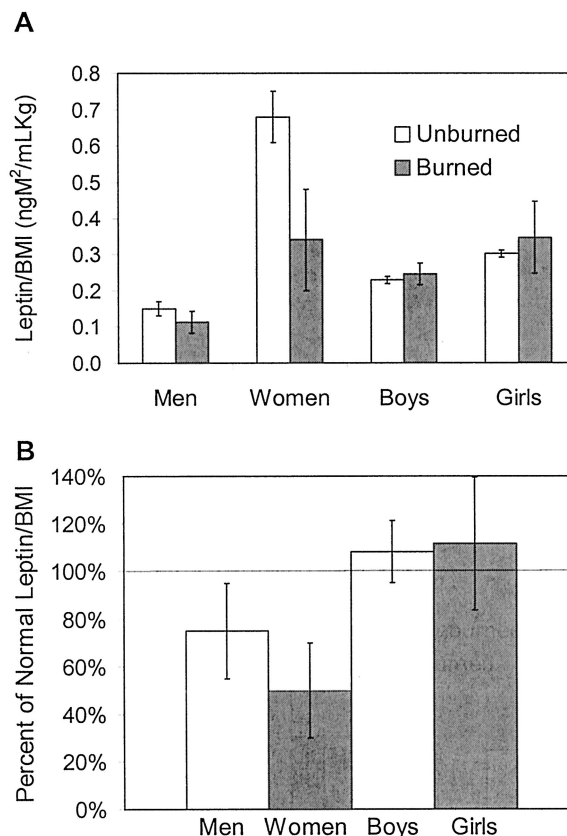


Figure 2. Normalized leptin concentrations by age and sex. A. Normalized mean circulating leptin concentrations in normal, healthy controls ($n = 13$ women, 11 men, 343 girls, and 446 boys)^{22,23} compared with those in burned patients. $P = .04$ for burn patients as a group compared with control patients; $P = \text{NS}$ for individual groups. B. Normalized mean circulating leptin concentrations for burned subjects expressed as a percentage of normal values. Leptin concentrations overall did not change significantly in burned patients compared with controls. In burned adult females, leptin concentrations tended to be lower than in healthy controls, but this difference was not statistically significant. This contrasts the findings of previous studies of elevated levels in septic patients. BMI, body mass index.

cantly different from those of unburned subjects ($75 \pm 20\%$ of normal, $P = .31$). Leptin levels for children of both sexes were not different from previously published normal levels for their sex and age²³ ($108 \pm 13\%$ and $112 \pm 28\%$ of normal for boys and girls with burns, respectively).

To examine the diurnal pattern of circulating leptin concentrations in burn patients, we determined the percent increase of leptin from the expected nadir at 12:00 PM to the expected peak at 2:00 AM. In 18 healthy women, the mean circulating plasma leptin level was increased by $56.4 \pm 8.5\%$ ($P < .0001$) from

12:00 PM to 2:00 AM. We report the results of women that were tested in the laboratory of P.J.H. because the same assays were used as for the burn patients. The same magnitude of change has been published for men and women.²⁵⁻²⁸ The diurnal increase of leptin was absent in the 20 burn patients (Figure 3). The mean increase of leptin between 12:00 PM and 2:00 AM in burn patients was only $6.1 \pm 4.4\%$, and this increase was not statistically significant. Thus, the normal leptin diurnal variation was completely lost in burned patients compared with healthy control subjects ($P < .0001$).

Cortisol

Mean plasma cortisol levels (Figure 4) in burn subjects (20.4 ± 1.0 mg/dL) were significantly higher than cortisol levels in normal subjects (9.8 ± 1.6 mg/dL), an increase of $108 \pm 10\%$ ($P < .0001$). This increase was similar for all age and gender groups. Although plasma cortisol decreases (Figure 5) by $54.4 \pm 8.7\%$ ($P < .0001$) between 12 PM and 2:00 AM in healthy subjects,¹¹ the decline in plasma cortisol levels was blunted to only a $13.9 \pm 3.7\%$ change ($P < .0025$) in the burn subjects ($P < .0001$ vs controls). Finally, there was no relationship between plasma leptin levels (normalized for BMI) and mean cortisol levels ($R^2 = 0.06$, $P = .32$) in burn patients (Figure 6).

Insulin and Glucose

Plasma insulin concentrations were significantly elevated in burn patients, with a mean 33.1 ± 4.0

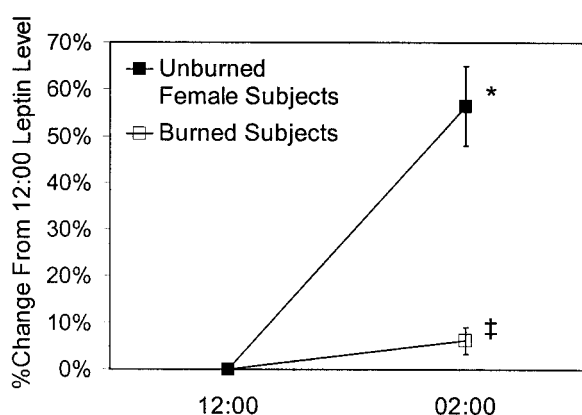


Figure 3. Change in mean leptin concentrations from nadir (12:00 PM) to peak (2:00 AM) in burned and unburned patients, expressed as a percentage of 12:00 PM level. Leptin secretion in burned patients loses its normal diurnal rhythm, with no detectable difference between circulating concentrations at the time of the normal peak and at the nadir. * $P < .0001$ vs 12:00 value. ‡ $P = NS$ vs 12:00 PM value; $P < .0001$ vs unburned subjects.

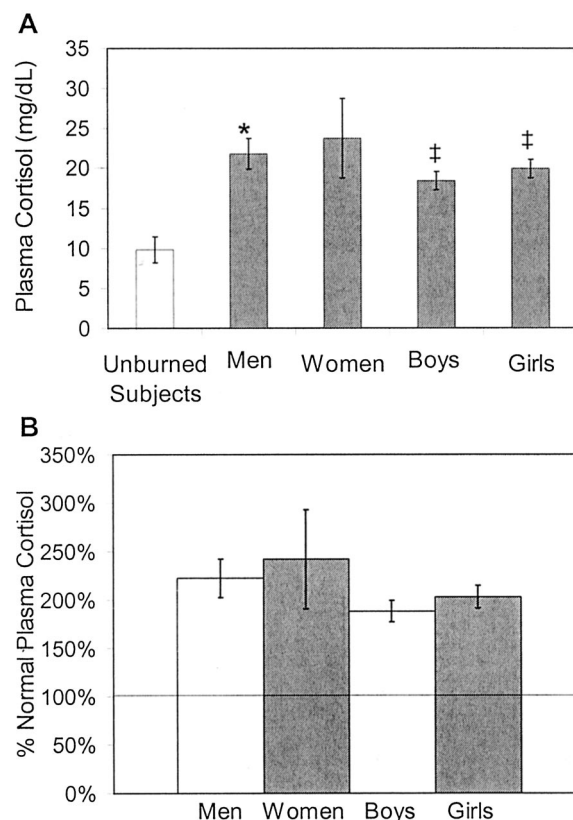


Figure 4. A. Mean circulating cortisol concentrations in normal, healthy controls compared with cortisol concentration in patients suffering from burn injury. B. Mean circulating cortisol concentrations for burn subjects expressed as a percentage of normal values. Cortisol concentrations are elevated to more than twice normal concentrations after burn injury, which concurs with previously published findings. * $P < .01$ vs normal healthy controls. ‡ $P < .0001$ vs normal healthy controls.

$\mu\text{U/mL}$ in burn subjects compared with 8.8 ± 1.1 $\mu\text{U/mL}$ in unburned men and women ($p < .0001$). This represents a $289 \pm 44\%$ increase in plasma insulin in burn subjects when compared with control subjects. No correlation between plasma insulin levels and plasma leptin or leptin adjusted for BMI was found ($R^2 = 0.07$, $P = 0.25$; see Figure 7). Plasma glucose levels also were increased in burned patients, with a mean glucose of 130.8 ± 4.9 mg/dL in burned patients compared with 88.4 ± 0.6 mg/dL in normal subjects ($P < .0001$). Interestingly, the insulin-to-glucose ratio also was dramatically increased in the burned subjects compared with normal healthy controls (0.26 ± 0.03 compared with 0.11 ± 0.01 , $P < .0001$), suggesting the presence of insulin resistance or an increase in counter-regulatory glucagon levels in the burn patients. Glucagon levels, however, were not determined in this study.

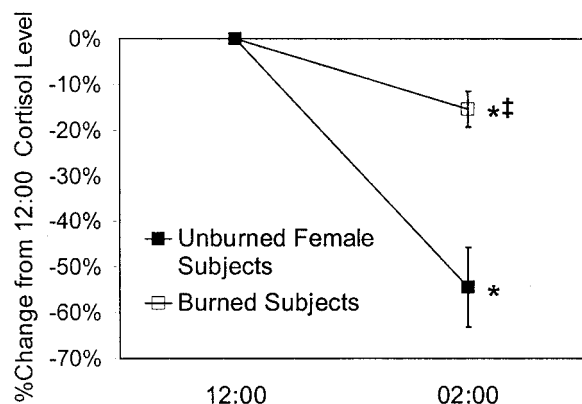


Figure 5. Change in mean cortisol concentrations from approximate peak (12:00 PM) to nadir (2:00 AM) in burned and unburned patients, expressed as a percentage of 12:00 PM concentration. The diurnal variation of cortisol secretion, although still present in burned patients, is severely blunted. * $P < .01$ vs 12:00 value. ‡ $P < .0001$ vs unburned subjects.

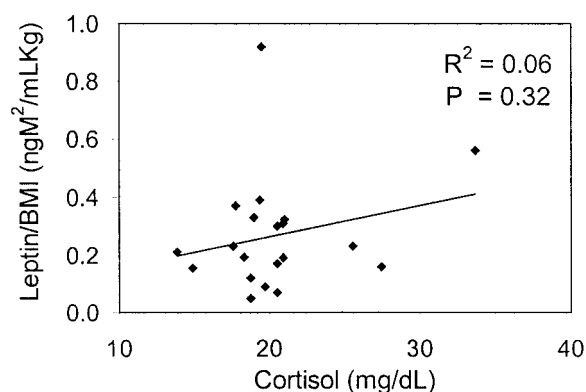


Figure 6. Relationship of mean normalized circulating leptin concentrations to mean cortisol concentrations in patients suffering from burn injury. Unlike previous reports in septic patients, no correlation exists between cortisol and leptin after burn injury. BMI, body mass index.

DISCUSSION

The mechanisms that regulate endogenous leptin secretion are the subject of considerable research efforts. Although body adiposity is a major determinant of circulating leptin concentrations,^{23,24,30} numerous studies have demonstrated that circulating leptin levels decrease in response to fasting or when caloric expenditure exceeds intake. Conversely, leptin levels also increase in response to overfeeding independently of changes of body fat.^{22,31} Despite the presence of burn injury, a positive correlation between BMI and leptin levels was found among the patients

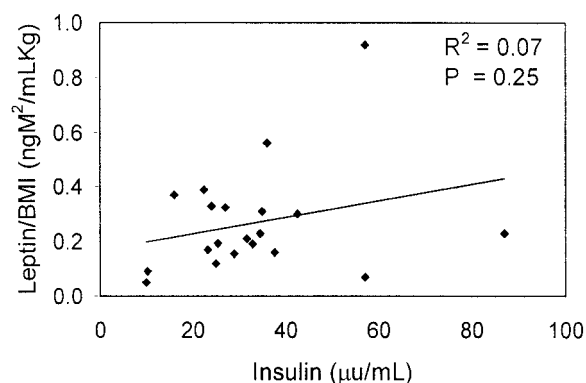


Figure 7. Relationship of mean normalized circulating leptin concentrations and insulin levels in patients with burn injury. No correlation exists between leptin and insulin levels after burn injury. BMI, body mass index.

in this study. Women are known to have higher circulating leptin concentrations than men and boys.^{22,23,32} This elevation persists even when controlling for the increased percentage of body fat in women compared with men or for female reproductive status (ie, menopause or hormone replacement therapy).³² In the present study in burn patients, adult women had leptin levels adjusted for BMI (leptin/BMI) that were significantly greater than those of the adult male subjects (0.34 ± 0.14 compared with 0.10 ± 0.03 , respectively).

One of the more prominent results from this study is the finding that circulating leptin levels were not elevated in burn patients. As previously discussed, several studies have examined leptin levels in patients suffering from sepsis and have reported circulating leptin levels as much as five times higher than in healthy control subjects.¹⁵⁻¹⁷ In contrast, burn patients, although also critically ill, had circulating leptin levels lower than those of normal lean subjects. This response was most marked in the adult female subjects. One possible explanation for the discrepancy between the current study and previous studies is that none of the studies in septic patients controlled for differences related to sex, and the majority also did not adjust for the differences in body composition by normalizing leptin for BMI. Furthermore, none of the studies in septic patients provided information on the timing and type of nutritional supplementation given to the subjects. All of these factors (adiposity, sex, and nutritional status) can have a marked influence on circulating leptin levels and may have affected the conclusions of those studies. In the current study, we controlled for the influence of adipose tissue mass by normalizing leptin levels for BMI. We also examined the influence of gender on circulating leptin in

burn patients to determine the contribution of the well-known sexual dimorphism. Furthermore, all patients in the current study received continuous nutritional supplementation at the time leptin levels were assessed. This supplementation would be expected to raise the subjects' insulin levels and, therefore, increase their leptin levels.

Nonetheless, circulating leptin levels in burn patients were significantly lower than those of healthy, fasting control subjects. This change was attributed to the decreases found in adult women. A possible explanation for the lower absolute and adiposity-adjusted leptin is provided by the observed increase of the insulin to glucose ratio in the burn patients suggesting the presence of marked insulin resistance which would be expected to decrease adipocyte leptin production.³ Lower leptin levels, as observed in burn patients in this study, have been associated with an increase in subjective sensations of hunger.⁷ Our patients demonstrated lower-than-average circulating leptin levels. It is therefore unlikely that the mean circulating leptin levels, per se, are responsible for the anorexia that complicates burn injury convalescence.

Another striking finding among burn subjects was the loss of diurnal variation in leptin levels. Previous studies have demonstrated a diurnal pattern of leptin secretion in healthy subjects with a nadir that typically is observed between 10:00 AM and 12:00 PM and a nocturnal peak between midnight and 2:00 AM.³³ This pattern, however, rather than being circadian in nature like the cortisol rhythm, is more closely entrained to the daily cycle of caloric ingestion. Schoeller et al¹⁰ demonstrated this relationship in a study in which they were able to shift the timing of the leptin peak but not the cortisol peak by altering meal timing. We suspect the continuous nature of the nutritional supplementation received by all patients in this study is a major factor contributing to this loss of diurnal variation. Although normal healthy subjects demonstrated a greater than 55% increase of circulating leptin between 12:00 PM and 02:00 AM, burned subjects exhibited less than a 7% increase. It is likely this continuous nutritional supplementation results in a continuous elevation of insulin levels rather than discretely timed peaks associated with meal ingestion,¹¹ which would be expected to lead to a loss of the normal diurnal pattern of circulating leptin.

The loss of normal leptin rhythm also was noted in a study of septic patients, although in that study, the loss of normal rhythm was associated with significantly elevated leptin levels.¹⁵ Although decreases of fasting plasma leptin concentrations in women produced by a prolonged, moderately energy-restricted diet were related to increased sensations of hunger,⁷

no published studies to our knowledge have specifically examined the relationship of the diurnal leptin pattern to sensations of hunger. However, it is possible that the amplitude of the diurnal pattern is an important signal of recent energy intake to the central nervous system. If so, it is possible that the loss of normal diurnal pattern in leptin levels at least partially contributes to anorexia commonly observed in burn patients.

Cortisol levels also are known to increase in response to many conditions associated with physiologic and psychologic stress, including burn injury.² The burned subjects in our study exhibited average cortisol levels more than twice those of normal unburned subjects. This increase is comparable with the findings of previously published studies of cortisol levels both in septic and in burned patients.^{2,34} Likewise, the diurnal variation of cortisol secretion was blunted in burned patients, which also has been demonstrated in studies of septic patients.¹⁵ Some studies have reported an inverse correlation between circulating leptin and cortisol levels.¹⁵ One potential mechanism for the inverse relationship could be that leptin may suppress cortisol production.^{35,36} However, other findings suggest no relationship between leptin and cortisol exists.³³ In the present study, we did not observe any correlation between cortisol levels and leptin levels in the burned patients. The precise relationship between cortisol and leptin secretion remains unclear.

Also of significance, plasma insulin concentrations in burn patients were elevated to levels four times those of normal subjects. This is likely to be partly a result of the method of nutritional supplementation. Although insulin levels in control subjects were determined after an overnight fast, plasma insulin was assessed in the burned patients while they were receiving continuous tube feedings. Thus, all burned patients received continuous caloric input, including glucose and amino acids, both of which stimulate insulin secretion. The continuous tube feedings also are likely responsible for the persistently increased glucose levels observed in the burned patients. In addition, the difference between the expected morning nadir and nocturnal peak of leptin concentrations, which is dependent on insulin responses to meal ingestion,^{10,11} was reduced to such a degree in burn patients that the normal diurnal pattern was completely eliminated. This reduction is consistent with the observation that continuously infusing glucose at a low rate prevents the decrease of circulating leptin levels in fasting subjects but also blunts the expected diurnal pattern.⁹

CONCLUSION

Burn patients exhibit several characteristics typically observed after leptin administration in animals, including anorexia and a markedly increased metabolic rate. However, leptin levels in patients after burn injury appear to be normal to decreased, which contrasts findings in patients suffering from sepsis. However, as is observed in septic patients, burn victims do lose the normal diurnal pattern of circulating leptin levels. Although the ramifications of these findings are not clear, they suggest that other factors than leptin control the anorexia of burn injury. The loss of the diurnal leptin pattern most likely results from a combination of the continuous nutritional supplementation and the significant degree of insulin resistance observed in burned patients. Potentially, changes in the timing of the feeding regimen to better approximate normal meal times could reproduce meal-induced insulin and glucose excursions and therefore normalize the diurnal pattern of circulating leptin concentrations. A more thorough understanding of the endocrine and metabolic mechanisms underlying anorexia after burn injury will undoubtedly allow burn care providers to improve their ability to treat this challenging group of patients.

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